

SPL Process Meeting

Meeting Minutes

February 12, 2014

Chair of today's meeting: Pat Cowall-Hanover

Teleconference information:

USA Toll-Free 866-213-2145

USA Paid/International: 609-454-9913

Access code: 273 8216

Teleconference information: How to mute/unmute

#6: Mute

*6: Unmute

Link to the SPL wiki:

<http://spl-work-group.wikispaces.com/share/view/51351516>

Outstanding questions from previous meeting on New Implementation Procedure

1. Combination products:

- New data element on SPL resources page – Combination Product Type: see list of data values.

Combination Product Types

Source: National Cancer Institute Thesaurus

NCI Thesaurus OID: 2.16.840.1.113883.3.26.1.1

SPL Acceptable Term	Code
Type 0: Not a Combination Product	C112160
Type 1: Convenience Kit of Co-Package	C102834
Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)	C102835
Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)	C102836
Type 4: Device Coated/Impregnated/Otherwise Combined with Drug	C102837
Type 5: Device Coated or Otherwise Combined with Biologic	C102838
Type 6: Drug/Biologic Combination	C102839
Type 7: Separate Products Requiring Cross Labeling	C102840
Type 8: Possible Combination Based on Cross Labeling of Separate Products (Temporary Type)	C102841
Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	C102842

- Melanie Benson: For classification Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.) – does this mean an already approved PFS which was approved as a simple contain-closure supplement back in the 90's will now be considered under this code, or is this for product approved specifically as a combination product?
- Question 2: We need to ask Lonnie to discuss what this means.
 - o This may cover all products and may highlight what is defined as a kit.
 - o Does this cover only those products that cross divisions...or a single division.

Response from Lonnie: Combination products are defined in 21CFR 3.2 (e) (1). Thus you should consider your product in light of these definitions.

CFR 3.2 has the description of the combination products:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=3.2>.

Also, this is really a regulatory question. You should contact your regulatory division to further clarify.

2. Vicki Vos (Baxter): I still have issues with the Revised Date at the end of the Highlights section within a PLR as to how this is determined. As discussed before in these meetings I was under the impression that this is now being pulled from the most recent update to sections 1 – 17, as per the attached copy of the meeting minutes:

,

Changes include the following (additional information added per followup with Lonnie:

- Rendering of most recent highlights text revision date excluding Data Elements Section and all sections past section 17.
 - highlights revision date no longer being pulled from effective time – it's pulled from whatever section was changed most recently
 - The highlights date will pick up latest revision date in sections 1-17.

Question: In the new validation procedure, if I am reading this correctly on pages 22-23 under "Highlights and labeling boilerplate items included", it states that the revised date is taken from the effective time. My question, is when I think of "Effective Time" that is the date that is entered into the "Labeler, Registrant, and Establishment Information" under "Effective Date". So based off of this, it is still being pulled from the Effective Time?

Any help in understanding where this date is being pulled from so that I can communicate this out correctly is greatly appreciated.

Discussion:

- Question for Lonnie: Section 2.2.4. Is this working as previously discussed. Was there an oversight in the validation document – ie t
- FDA stylesheet pulls the date from Sections 1-17

- DailyMed just switched their style sheet over to using Section 1-17

Response from Lonnie: Your understanding of the process is correct. The style sheet creates the date in the highlights from the most recent effective time in sections 1-17. The validation document simply states the effective time – and in this case, it means the effective time of the appropriate section.

3. Chad (Reed): There is a new validation procedure that checks that the ingredients match previous submissions that use an application numbers.
 - Real reason behind this – several companies are submitting under the same application number but using different ingredients.
 - What error is this trying to catch? They want to make sure that all companies manufacturing product under the same application are reporting the same data/ingredients for the application (relabelers, manufacturers, etc) Consistency.
 - Question for Lonnie: What happens if there are multiple records already on Daily Med that have this error. Which one will be used as the primary record?
 - Validation section number: 3.1.7.26. Page 43. Newly implementation rules will improve quality of data on Daily Med.
 - Kathy Lins: One of their products is used as a component in 101 kits—from numerous other manufacturers. Thus, the validation procedure will make sure that all of the kits report the active ingredient consistently with what is reported by their application drug listing.

Response from Lonnie: The goal is to make the data consistent and correct. There is no primary record. If a manufacturer submits data that is correct, they need to ask for a manual override. Then there file will serve as the last record. It will be correct and will serve as the basis for future comparison.

Product Content files – future attraction!!!! This is a new report that will provide information on the active ingredients for all products. Eventually you will be able to check your data against the primary content. This is currently being reviewed within FDA. It will eventually be posted to Daily Med.

New Questions:

4. New SPL data requirement for combination products - timing. We discuss this change at the meeting in January. SPL vendors have been alerted to this before the recent announcement, and your software should either already been updated or should be updated to accommodate this change.

Beginning **May 1, 2014**, SPL files with the [biologic regulated] document types listed directly below will be validated for inclusion of the combination product category data element:

- Cellular Therapy
- Licensed Minimally Manipulated Cells
- Non-standardized Allergenic
- Plasma Derivative
- Standardized Allergenic
- Vaccine Label

In addition, SPL files which include an application number preceded by “BA” or “BN” are included this first phase (described above.)

Beginning **September 1, 2014**, SPL files with the CDER-regulated document types listed directly below will be validated for inclusion of the combination product category data element:

Question: When was the new SPL validation requirement first announced to the public? Ie when were Pharma companies and SPL software vendors first aware of this requirements.

- This has been discussed extensively by FDA:
 - Lonnie went over the specs with vendors for this in January 2013.
 - Lonnie did a good job emphasizing this to the vendors in the validation session review in January, 2014.
- Background: CDRH released their proposed listing rule in 2010. Comment #7 in the preamble. CDRH is intended to find a process to identify combination product. So this is part of their process.
- Implementation: CBER (vaccines) in May, CDER products in September,
 - Goal: to collect a list of combination products.
 - If the vendor software already accommodates, then you can submit CDER products during the transition period.
 - They can accept it before May 1st if you really want it.
 - Not included:
 - Cosmetics and medical food is 100% voluntary. They do not submit listing documents – and are not included in the validation procedure.
 - Bulk ingredients – most are not combination products.
 - CVM will not follow this – they have a different process.
 - Validation data should be checking to make sure that the data is there. There is no validation against an internal FDA list that the products are recording this data correctly. The intent of this information is to help identify combination products.

5. Tricia Pazeck (Perigo): They have been asked to change their dosage form in the SPL. Is this a new review procedure?

Lonnie: If you ask for an override and/or they notice that a dosage form does not match the definition of dosage form, FDA will ask you to correct it. This is a service because this will eventually be checked as part of the product content report.

6. Kathy Lins: Annual reportable updates to SPL documents.
- Does anyone know if there is anything in a SPL Guidance that talks about when to submit annual reportable SPL updates?
 - Do most companies follow the CFR that states updates should be made in June and December? Or do companies submit AR updates every time they occur? Or do you wait until just before the AR is due to submit the most recent AR updates (which could be multiple updates that have occurred throughout the year)?

I would like to hear how other companies handle annual reportable updates?

Response from Lonnie: In regards to the question about submitting SPL files with annual reports, the answer is in the responses to questions 2 and 34 of this guidance document:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

Question 34:

Applicants should submit an SPL file of the content of labeling with an annual report if an SPL file has not previously been submitted for the application, or if there have been changes to the content of labeling since the last submission of final SPL. If there have been no changes since the last submission of final SPL, then the annual report can include a reference to the electronic content of labeling previously submitted.⁶

⁶Final SPL is the submission of SPL that is in current use. This includes SPL with approved content of labeling submitted subsequent to the approval of an original BLA/NDA or prior approval supplement; SPL submitted to a CBE supplement (with the initial submission and any subsequent amendments); and SPL submitted to an annual report that contains “annual reportable” changes made since the last submission of final SPL.

The June and December dates are for drug listing submissions.

- Lilly: We submit information as they occur.
- FDA: FDA wants real time updates – so that data on Daily Med is as updated as possible.

Consideration: Also, see the Feb 2013 guidance on “Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements” -- states that the revision date in the Highlights should be the date of submission to FDA.

- BMS interprets “submission” to include drug listing submissions to the FDA. Thus they use the implementation date on the USPI. They submit the SPL to the review division at the time as the annual report.
- Goal is to keep the SPL as current as possible.

7. **Janet V. DeLuca:** We have an annual reportable update to the package label, (PDP). Are we required to update the DailyMed with this update; if so, do we also need to update the actual package insert because the PDP is not shown on the paper version of the PI.

You should update the SPL for changes to the PDP section as they are implemented, and submit drug listing concurrently. Thus the most recent information is posted to Daily Med. This is consistent with FDA guidance (2009) - to updates to labeling should be drug listed in real time – ie as they happen – instead of 21CFR207 which says to update in June and December.

8. **Revision Dates on labeling:** Following these last 2 questions, there was a general discussion of how companies manage revision dates in various labeling pieces and SPL effective times. Following is a summary of the discussion and various business practices:

Annual reportable changes:

- FDA guidance titled “Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements:
For annual report labeling, the revision date should reflect the date that the revised labeling is submitted to FDA.
- In the past, companies have submitted AR changes once a year. However, with this new guidance and availability of electronic submission, many companies submit AR changes as they happen – especially to allow use of real time revision dates.
- Companies base the revision date on implementation of change (USPI, PPI, carton/label): this is subject to individual company practices.
 - o Many companies interpret it as the date that the change is made public (ie via posting to their website and/or druglisting the SPL).
 - o Some companies go the extra step to monitor when the change is first used in production/packaging – revision is the forecasted date that the change will be used in packaging or the date in which the old packaging can no longer be used.
 - o Some companies go the extra step to forecast when the change is in the supply chain.

CBE changes:

- FDA guidance titled “Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements:
For CBE supplement labeling, the revision date generally is the date of application receipt.....If the labeling text is changed by FDA, the revision date will be changed to the date of CBE approval.
- Most companies drug list revised SPL immediately upon submission.

PAS changes:

- FDA guidance titled “Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements:
...*the revision date would be the date of application approval*.....
- FDA Approval letters state to drug listing within 14 days.

Drug listing only changes (supply chain or drug product data):

- Changes are drug listed as they are implemented (and/or we find out about them)
- Many companies review their SPL periodically (eg annually at the time of the annual report, and/or at a label change.)
- Some companies bundle smaller changes and hold them for June/December.
- Timing may be influenced by type of change how big a change this is:
 - o Content changes are typically drug listed sooner
 - o Supply chain: changes that affect import
 - o Manufacturing spec changes are not as important to change in real time.
- Revision dates on labeling:
 - o If there are no other changes to the labeling, when these “drug listing” changes are made, the revision dates in the labeling itself do not change. ie The date in the highlights section does not change. It remains the revision date of the USPI.
- The effective time of the SPL
 - o This date changes to the current date. This is reflected by the date that is displayed at the end of the SPL.

Revision Dates on the various labeling pieces when changes are made to one or more pieces of labeling (ie USPI, PPI, MedGuide, IFU)

- The revision date each labeling piece is independent of each other
 - o USPI: The revision date of the USPI is the last approval date (or CBE date or AR date) for the USPI itself. This date appears in the highlights section.
 - o PPI/MedGuide: Approval/CBE/AR date of the PPI/MedGuide
 - o IFU: Approval/CBE/AR date of the IFU
- Note: Date in the highlights is always the revision date of the USPI
- There may be several dates on the printed piece (if printed USPI is printed together with the PPI).
 - o Revision date of each labeling piece
 - o Revision date of the artwork – this is usually the date of the latest revised labeling included in the artwork.
- Date at the end of the SPL is the revision date of the SPL
-
